

THAT WHICH IS CLAIMED:

1. A method for treating a human subject for an inflammatory disease or autoimmune disease, comprising administering to said subject an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said monoclonal antibody being free of significant agonist activity when bound to the CD40 antigen expressed on the surface of said cell, said human anti-CD40 monoclonal antibody being selected from the group consisting of:
- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
  - b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
  - c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
  - d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
  - e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
  - f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
  - g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

5 j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

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2. The method of embodiment 1, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity ( $K_D$ ) of at least about  $10^{-6}$  M to about  $10^{-12}$  M.

3. The method of embodiment 1, wherein said fragment is selected from the  
15 group consisting of a Fab fragment, an  $F(ab')_2$  fragment, an Fv fragment, and a single-chain Fv fragment.

4. The method of embodiment 1, wherein said inflammatory disease or  
autoimmune disease is selected from the group consisting of systemic lupus erythematosus  
20 (SLE), discoid lupus, lupus nephritis, sarcoidosis, juvenile arthritis, rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis, gouty arthritis, rejection of an organ or tissue transplant, graft versus host disease, multiple sclerosis, hyper IgE syndrome, polyarteritis nodosa, primary biliary cirrhosis, inflammatory bowel disease, Crohn's disease, celiac's disease (gluten-sensitive enteropathy), autoimmune hepatitis,  
25 pernicious anemia, autoimmune hemolytic anemia, psoriasis, scleroderma, myasthenia gravis, autoimmune thrombocytopenic purpura, autoimmune thyroiditis, Grave's disease, Hashimoto's thyroiditis, immune complex disease, chronic fatigue immune dysfunction syndrome (CFIDS), polymyositis and dermatomyositis, cryoglobulinemia, thrombolysis, cardiomyopathy, pemphigus vulgaris, pulmonary interstitial fibrosis, sarcoidosis, Type I  
30 and Type II diabetes mellitus, type 1, 2, 3, and 4 delayed-type hypersensitivity, allergy or allergic disorders, asthma, Churg-Strauss syndrome (allergic granulomatosis), atopic

dermatitis, allergic and irritant contact dermatitis, urticaria, IgE-mediated allergy, atherosclerosis, vasculitis, idiopathic inflammatory myopathies, hemolytic disease, Alzheimer's disease, and chronic inflammatory demyelinating polyneuropathy.

5           5.       A method for treating a human subject for an inflammatory disease or autoimmune disease, comprising administering to said subject an effective amount of an antagonist anti-CD40 monoclonal antibody that specifically binds Domain 2 of human CD40 antigen, wherein said antibody is free of significant agonist activity when bound to Domain 2 of human CD40 antigen.

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6.       The method of embodiment 5, wherein said antibody is a human antibody.

7.       The method of embodiment 5, wherein said antibody is recombinantly produced.

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8.       The method of embodiment 5, wherein said antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line 12.12.

20           9.       The method of embodiment 5, wherein said antibody is selected from the group consisting of the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5542 and the antibody produced by the hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA-5543.

25           10.      The method of embodiment 5, wherein said antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

30           11.      The method of embodiment 5, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

12. The method of embodiment 5, wherein said antibody is selected from the group consisting of:

a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in  
5 SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group  
10 consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

d) a monoclonal antibody that binds to an epitope comprising residues 82-87  
15 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay;

f) a monoclonal antibody of any one of preceding items a)-e), wherein said antibody is recombinantly produced; and

20 g) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-f), where the fragment retains the capability of specifically binding to said human CD40 antigen.

25 13. The method of embodiment 5, wherein said inflammatory disease or autoimmune disease is selected from the group consisting of systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, sarcoidosis, juvenile arthritis, rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome, ankylosing spondylitis, gouty arthritis, rejection of an organ or tissue transplant, graft versus host disease, multiple sclerosis, hyper IgE  
30 syndrome, polyarteritis nodosa, primary biliary cirrhosis, inflammatory bowel disease, Crohn's disease, celiac's disease (gluten-sensitive enteropathy), autoimmune hepatitis,

pernicious anemia, autoimmune hemolytic anemia, psoriasis, scleroderma, myasthenia  
gravis, autoimmune thrombocytopenic purpura, autoimmune thyroiditis, Grave's disease,  
Hashimoto's thyroiditis, immune complex disease, chronic fatigue immune dysfunction  
syndrome (CFIDS), polymyositis and dermatomyositis, cryoglobulinemia, thrombolysis,  
5 cardiomyopathy, pemphigus vulgaris, pulmonary interstitial fibrosis, sarcoidosis, Type I  
and Type II diabetes mellitus, type 1, 2, 3, and 4 delayed-type hypersensitivity, allergy or  
allergic disorders, asthma, Churg-Strauss syndrome (allergic granulomatosis), atopic  
dermatitis, allergic and irritant contact dermatitis, urticaria, IgE-mediated allergy,  
atherosclerosis, vasculitis, idiopathic inflammatory myopathies, hemolytic disease,  
10 Alzheimer's disease, and chronic inflammatory demyelinating polyneuropathy.

14. A method for treating a human subject for transplant rejection, comprising  
administering to said subject an effective amount of a human anti-CD40 monoclonal  
antibody that is capable of specifically binding to a human CD40 antigen expressed on  
15 the surface of a human CD40-expressing cell, said monoclonal antibody being free of  
significant agonist activity when bound to the CD40 antigen expressed on the surface of  
said cell, said human anti-CD40 monoclonal antibody being selected from the group  
consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- 20 b) the monoclonal antibody produced by the hybridoma cell line 5.9 or  
12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from  
the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in  
SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ  
25 ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID  
NO:8;
- d) a monoclonal antibody comprising an amino acid sequence selected from  
the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in  
SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ  
30 ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID  
NO:5;

- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- 5 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- h) a monoclonal antibody that binds to an epitope comprising residues 82-89  
10 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and
- 15 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

15. The method of embodiment 14, wherein said treatment further comprises  
20 administering an immunosuppressive agent in a pharmaceutically acceptable excipient.

16. The method of claim 15, wherein the immunosuppressive agent is selected from the group consisting of cyclosporine, FK506, rapamycin, corticosteroids, CTLA4-Ig, and anti-B Lymphocyte Stimulator antibody.

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17. A method for treating a human subject for rheumatoid arthritis, comprising administering to said subject an effective amount of a human anti-CD40 monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said monoclonal antibody  
30 being free of significant agonist activity when bound to the CD40 antigen expressed on

the surface of said cell, said human anti-CD40 monoclonal antibody being selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or  
5 12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID  
10 NO:8;
- d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID  
15 NO:5;
- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- 20 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- h) a monoclonal antibody that binds to an epitope comprising residues 82-89  
25 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; and further administering an immunosuppressive agent in a pharmaceutically acceptable excipient.

18. The method of claim 17, wherein the immunosuppressive agent is selected from the group consisting of cyclosporine, FK506, rapamycin, corticosteroids, CTLA4-Ig, an anti-CD20 antibody, and anti-B Lymphocyte Stimulator antibody.

19. A method for treating a human subject having an inflammatory disease or autoimmune disease comprising administering to said subject an effective amount of a human monoclonal antibody that is capable of specifically binding to CD40 antigen, said monoclonal antibody being free of significant agonistic activity, wherein said antibody is the monoclonal antibody CHIR-5.9 or CHIR-12.12.